Prophylactic clip closure clarified: the question is not whether to clip, but when

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Hemostatic clips are established as effective to control active colonic bleeding[1], to prevent delayed perforation after endoscopic mucosal resection (EMR) induced deep mural injury[2], and to close free perforations occurring during EMR[3] and endoscopic submucosal dissection (ESD)[4]. A common use of clips has been prophylactic closure of colorectal polypectomy sites, with intent to prevent delayed hemorrhage. This use of clips is controversial, because efficacy data on prophylactic clipping are mixed, and clips are expensive. Delayed hemorrhage is the most common complication of colonoscopy, and is related to large lesion size, proximal location, and use of antithrombotic agents post procedure[5]. In this and the next issue of Gastroenterology, three randomized controlled trials (RCTs)[6-8], two showing a benefit[6, 7] and one with no benefit[8], clarify when prophylactic clipping has value.

The negative trial (no clipping benefit) by Feagins et al.[8] was performed by general endoscopists at four Texas Veterans Administration hospitals and involved 1386 polyps ≥ 1 cm in size in 1050 patients. Mean polyp size was 14 mm, 16% were ≥ 20 mm, and 30% were pedunculated. The trial was designed as an equivalence study and did not reach the intended sample size because of loss of funding, but the overall rate of delayed bleeding in the clipped group (2.3%) was similar to the control group (2.9%), with no benefit in any subgroups. The result supports two meta-analyses that found no benefit from prophylactic clipping[9, 10]. One consistent feature of negative trials of prophylactic clipping has been minimal bleeding in the control group[9, 10]. Thus, the first ever RCT had mean polyp size 7 mm, and a 0.4% control group delayed bleeding rate[11]. By comparison, the 2.9% control bleeding rate of Feagins et al. is relatively high, yet substantially lower than studies confined to nonpedunculated lesions ≥ 20 mm, where the right colon bleeding risk approaches or exceeds 10%[12, 13].

In contrast to the negative studies, each of several studies with a higher risk of bleeding in the control arm found benefit in prophylactic clipping (Table 1). This includes three RCTs, including two now

published in Gastroenterology[5, 6]. The RCT by Pohl et al. involved experienced colonoscopists in 18 mostly U.S. centers[6]. There were 919 patients, all with nonpedunculated lesions ≥ 20 mm removed by EMR. Clipping could not be performed in 13%, mostly due to large size, and 20% were only partially closed. Further, 10% of the control lesions were clipped, generally for fear of perforation or anticoagulation. In the intent to treat analysis, delayed bleeding occurred in 7.1% of the control group versus 3.5% with clipping (p=0.015). The benefit was confined to the hepatic flexure or proximal, with the control bleeding rate in the proximal colon 9.6%, vs. 3.3% with clipping (p=0.001). Mean time to bleeding was 1 vs. 7 days in the control vs. clipped group, suggesting that if clipped lesions bleed, they bleed when the clips fall off. The results were independent of lesion size, cautery setting and anti-thrombotic agents. The lack of association with size likely reflects that 20-40 mm defects are the easiest to close completely, and lesions over 40 mm are more likely to either be closed partly or not at all. Delayed perforation requiring surgery in 3 control and 0 clipped patients suggests another potential benefit.

The second new successful clipping RCT was performed by 11 experienced endoscopists at 11 hospitals in Spain[7], enrolling 235 nonpedunculated lesions ≥ 20 mm in size, mean size 37 mm, with 90% proximal to the splenic flexure. The investigators used a bleeding prediction score they developed[5] to enrich the study with lesions at high bleeding risk, resulting in a 12.1% delayed bleeding rate in the control group. In the clip arm, complete closure was achieved in 57%, partial in 28%, and 15% failed (no closure), with bleeding rates of 1.5%, 9.1%, and 11%, respectively. The complete closure group had an 89% reduction in delayed bleeding compared to controls. Only one of 35 transverse colon lesions in either arm bled.

We can now conclude that consistent evidence indicates that non-pedunculated lesions in the cecum, ascending or hepatic flexure that are ≥ 20 mm and removed by EMR with electrocautery should be

considered for prophylactic clip closure after resection, regardless of antithrombotic therapy. If complete closure is obtained (clips in close proximity and no or minimal submucosa still visible), the number needed to treat to prevent one delayed bleed is as low as 9.5. Lesions distal to the hepatic flexure or < 20 mm in diameter do not clearly benefit. Cold EMR (no electrocautery), seems effective in eradicating sessile serrated lesions (also called sessile serrated polyps and sessile serrated adenomas) of large size[14], and should not be followed by clip closure. The efficacy of cold EMR for large conventional adenomas is currently uncertain.

Questions remain about prophylactic clipping (Table 2). For example, all studies in Table 1 utilized 11 mm clips. Will larger clips improve efficacy? Another important question is whether there are subsets of lesions < 20 mm that warrant clip closure. For example, a recent study found that 7.3% of lesions < 10 mm removed by cold snaring in patients maintained on direct acting oral anticoagulants developed delayed bleeding [15].

Many patients with endoscopically resectable benign colon polyps are still being sent for surgical resection[16], despite higher mortality, morbidity, and cost with surgery[17, 18]. EMR is the clear first line treatment for large benign colorectal lesions and EMR methods are improving. For example, recent investigation has produced impressive improvements in decreasing polyp recurrence rates after EMR[19]. With the role of prophylactic clipping clarified, we can achieve lower complication rates after EMR of large right colon lesions, which should reduce fear of performing large right colon EMRs. Further, we can improve the cost-effectiveness of clipping by refraining from clip use after resection of low risk lesions where no benefit has been demonstrated.

Cost analyses of closing right colon EMR sites ≥ 20 mm will undoubtedly be conducted, but are unlikely to model the cost savings of more patients undergoing EMR and not surgery, or to appreciate that physicians are willing to spend more to avoid complications and reduce medical-legal risk. Wound closure is clearly a powerful concept. New, easily applied clips or alternative closure methods that are more effective and/or less expensive are needed. Until such tools are developed and validated, these randomized clinical trials published in *Gastroenterology* demonstrate that prophylactic hemostatic clip closure after EMR of right colon lesions ≥ 20 mm is effective in preventing delayed hemorrhage. EMR continues to become a safer and more effective treatment for large flat and sessile colorectal lesions.

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Table 1. The five studies establishing the effectiveness of hemostatic clip closure in preventing delayed bleeding from large (≥ 20 mm) endoscopic mucosal resection defects

Author	Year	Design	Number of patients or lesions	Lesion size	Delayed bleeding without clipping	Delayed bleeding with clipping	P value
Liaquat	2013	Historical controls	524	≥ 20 mm	9.7%	1.8% fully clipped 5.8% partly clipped	0.001
Zhang	2015	RCT	348	10-40 mm	6.9%	1.1%	0.01
Albeniz	2016	Prospective cohort	1,255	≥ 20 mm	3.9%	1.4%	0.018
Pohl	2019	RCT	919	≥ 20 mm	7.5% overall 9.6% proximal 1.4% left	3.5% overall 3.3% proximal 4.0% left	0.015 0.001 0.178
Albeniz	2019	RCT	235	≥ 20 mm	12.1%	5.0% 1.5% fully clipped 9.1% partly clipped 11% failed clipping	0.061 0.034

RCT: randomized controlled trial

Table 2. Some unanswered questions about prophylactic clip closure after EMR and polypectomy

- What are the key technical components of effective clip placement (clip spacing, amount of tissue enclosed in clip, etc.)?
- How cost-effective is prophylactic clip closure of defects after right colon EMR of ≥ 20 mm lesions?
- Are large (e.g. 16 mm) clips more effective than 11 mm clips?
- Does clip efficacy vary by manufacturer or design or retention rate?
- What is the relationship between the duration of clip retention on the site and prevention of bleeding?
- Are their subgroups of patients with lesions < 20 mm or left colon location that benefit from clipping?
- How does use of hemostatic clips compare to endoscopic suturing or over the scope clips for prevention of complications?
- Can general endoscopists achieve closure efficacy equal to that in clinical trials?

EMR- endoscopic mucosal resection